Automated and systematic revision of a large-scale signaling network model

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Introduction

Several groups have recently developed large-scale computational models for signaling networks, including T cells, cardiac myocytes, and fibroblasts[1-3] . Given their large scope, these models introduce new challenges in the model revision to improve model consistency with heterogeneous experimental data and to incorporate newly discovered pathways.

Automating the process of developing, evaluating and validating different versions of predictive models may enhance the speed and rigor of model revision.

Here, we developed a user-friendly framework to automatically create a logic-based differential equation (LDE) model[4], simulate the experiments, and compare the model results with available heterogeneous data for validation in two applications:

1) We first evaluate the approach with a toy model, identifying the main reactions that contribute to the prediction accuracy against idealized data.

2) We then apply the method to perform expanded experimental validation of our published cardiac hypertrophy model[2], quantify structural robustness, and systematically screen for potential improvements.

Applying Framework on a Toy Model

- Two formatted Excel spreadsheet as inputs for the automated validation software including 1) model specification and 2) measurement data.
- Responses were categorized qualitatively as as an increase, decrease, or no change compared to control.
- Simulating corresponding experiment conditions for each defined observation with supporting biochemical data by validation software
- Categorizing predictions based on a threshold change of ± 0.001 (units of fractional activation) compared to activation levels at the control state (no stimulation)
- Two minor modifications in previous LDE model[4] by changing the reactions weight factor from 1 to 0.9 and modifying the inhibition formula for having better predictions

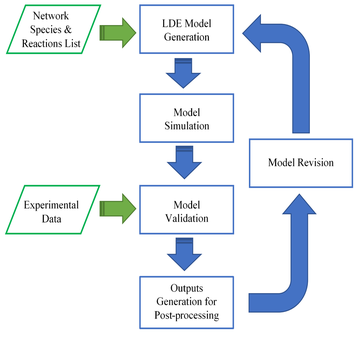

Figure 1. Framework Process Flow.

Table 1. Validation Result of Toy Model

Input	Input 2	Output	Measurement	Prediction
A		C	Increase	Increase
A		D	No Change	No Change
A		E	Increase	Increase
B		C	No Change	No Change
B		D	Increase	Increase
B		E	No Change	No Change
A	B	C	Decrease	Decrease
A	B	D	Increase	Increase
A	B	E	Decrease	Decrease

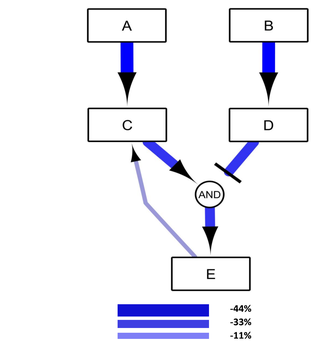

Figure 2. Identifying Main Reactions in Toy Model. The changes in percent of agreement between measurements and model predictions after knockout of each reaction.

Expanded Validation of Hypertrophy Model

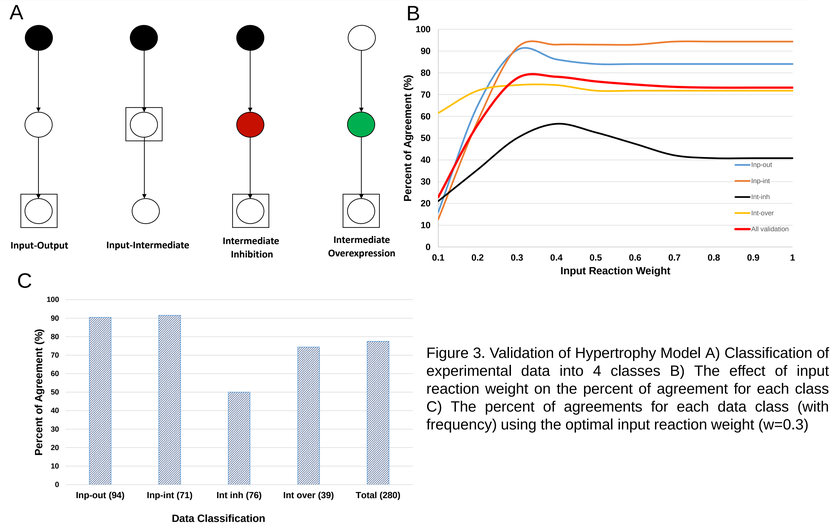

Figure 3. Validation of Hypertrophy Model A) Classification of experimental data into 4 classes B) The effect of input reaction weight on the percent of agreement for each class C) The percent of agreements for each data class (with frequency) using the optimal input reaction weight (w=0.3)

Example Experiment-Model Validations

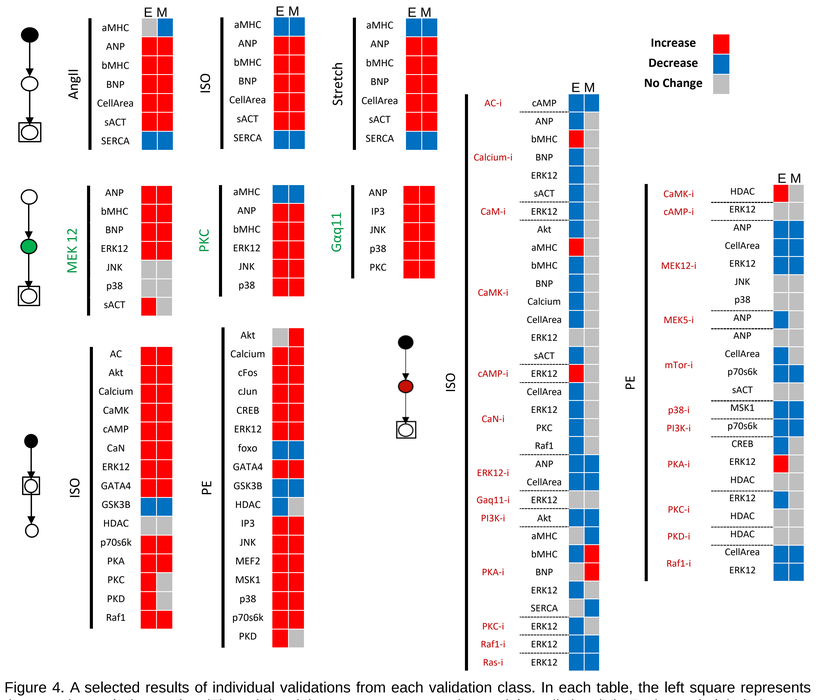

Figure 4. A selected results of individual validations from each validation class. In each table, the left square represents the experimental observation (E), and the right square represents the model prediction (M). Each row is labeled as the output that was compared to control.

Reactions Contributing to Model Accuracy

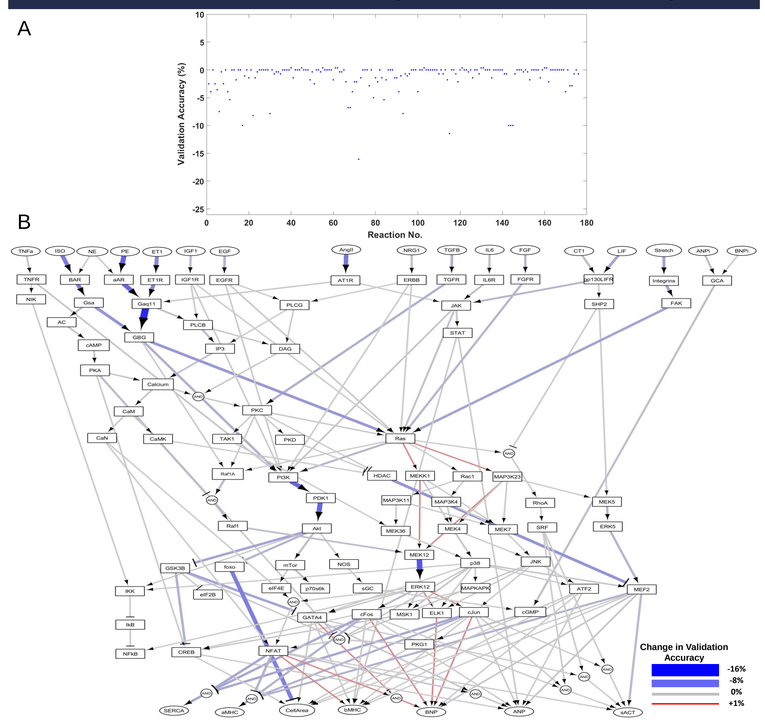

Figure 5. Single Reaction Knockout on Hypertrophy Network to identify the most important reactions. A, B) The changes in validation accuracy between literature-based experimental data (280 observations) and model predictions after knockout of each reaction.

Conclusion

The automated validation framework allows for a quick and user-friendly building and validation of large-scale signaling network models. This framework can be employed by various researchers to utilize diverse experimental data to systematically build, and revise their model to improve its reproducibility.

Acknowledgements

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References

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